This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Previously Cancelled).

2. (Currently Amended) A nucleic acid molecule comprising at least a first signal sequence and a second signal sequence and a recombinase gene operably linked to an expression control sequence, said first and second signal sequences being positioned to mediate ~~excision or~~ inversion of a sufficient portion of either the recombinase gene or the expression control sequence to inactivate or decrease recombinase activity when the first and second signal sequences are contacted with a recombinase, thereby decreasing or eliminating recombinase-mediated toxicity.

3. (Previously Amended) The nucleic acid molecule of claim 2, wherein said nucleic acid molecule is included in a retroviral vector and said signal sequence is inserted into a retroviral long terminal repeat of said vector.

4. (Originally Presented) The nucleic acid molecule of claim 3, wherein said signal sequence is inserted into the U3 region of the 3' retroviral long terminal repeat of said vector.

5. (Previously Amended) The nucleic acid molecule of claim 2, wherein said recombinase is selected from the group consisting of a *cre* recombinase and a Flp recombinase and the signal sequence is selected from the group consisting of lox sequences and FRT sequences.

6. (Previously Cancelled).

7. (Previously Amended) The nucleic acid molecule of claim 2, wherein said signal sequences flank said recombinase gene or said expression control sequence of said recombinase gene.

8. (Previously Amended) A cell comprising the nucleic acid molecule of claim 2.

9. (Originally Presented) The cell of claim 8, further comprising a second nucleic acid molecule comprising a target gene and signal sequences recognized by said recombinase.

10. (Currently Amended) The cell of claim 9, wherein said recombinase, when expressed in said cell, ~~excises or~~ inverts a sequence in said second nucleic acid molecule that is located between said signal sequences in said second nucleic acid molecule, and the ~~excision or~~ inversion results in modulation of expression of said target gene~~, thereby decreasing or eliminating recombinase-mediated toxicity~~.

11. (Currently Amended) The cell of claim 10, wherein said signal sequences in said second nucleic acid molecule are in inverted ~~direct~~ orientation with respect to one another.

12. (Currently Amended) The cell of claim 11, wherein said signal sequences in said second nucleic acid molecule flank said target gene, so that expression of said recombinase results in inversion ~~excision~~ of said target gene, and inactivation of expression of said target gene.

13. (Currently Amended) The cell of claim 11, wherein said signal sequences in said second nucleic acid molecule flank a positive regulatory element of said target gene, so that expression of said recombinase results in inversion ~~excision~~ of said positive regulatory element, and inactivation of expression of said target gene.

14. (Allowed) A cell comprising two nucleic acid molecules, wherein the first nucleic acid molecule comprises a recombinase gene operably linked to an expression control sequence and signal sequences recognized by a recombinase and the second nucleic acid molecule comprises a target gene and signal sequences recognized by a recombinase, wherein said signal sequences in said second nucleic acid molecule flank a negative regulatory element of said target gene, so that expression of said recombinase results in excision of said negative regulatory element, and activation of expression of said target gene.

15. (Allowed) A cell comprising two nucleic acid molecules, wherein the first nucleic acid molecule comprises a recombinase gene operably linked to an expression control sequence and signal sequences recognized by a recombinase and the second nucleic acid molecule comprises a target gene and signal sequences recognized by a recombinase, wherein said signal sequences in said second nucleic acid molecule are in an inverted orientation with respect to one another.

16. (Allowed) The cell of claim 15, wherein said signal sequences in said second nucleic acid molecule flank an inverted positive regulatory element of said target gene or an inverted coding

region of said target gene, so that expression of said recombinase results in inversion of said inverted positive regulatory element or inversion of said inverted coding region, and activation of expression of said target gene.

17. (Allowed) The cell of claim 15, wherein said signal sequences in said second nucleic acid molecule flank an inverted negative regulatory element of said target gene or a coding region of said target gene, so that expression of said recombinase results in inversion of said inverted negative regulatory element or inversion of said coding region, and inactivation of expression of said target gene.

18. (Originally Presented) The cell of claim 8, wherein said signal sequences in said nucleic acid molecule comprising said sequence encoding said recombinase flank said nucleic acid sequence encoding said recombinase.

19. (Originally Presented) The cell of claim 8, wherein said signal sequences in said nucleic acid molecule comprising said sequence encoding said recombinase flank a positive regulatory element of said nucleic acid sequence encoding recombinase.

20. (Originally Presented) The cell of claim 9, wherein said nucleic acid molecule comprising said sequence encoding said recombinase and said second nucleic molecule are present in the same vector.

21. (Allowed) A cell comprising two nucleic acid molecules, wherein the first nucleic acid molecule, comprising a recombinase gene operably linked to an expression control sequence and signal sequences recognized by a recombinase and the second nucleic acid molecule, comprising a target gene and signal sequences recognized by a recombinase, are present in separate vectors.

22-50. (Cancelled).

51. (New) The nucleic acid molecule of claim 2, wherein said signal sequences are in inverted orientation with respect to one another.

REMARKS

Claims 2-5, 7-21 and 51 are pending in the present application. Claims 22-50 have been cancelled. Claims 2 and 10-13 have been amended. Claim 51 has been added. Claims 14-17 and 21 have been allowed. No new matter has been added.

RESPONSE TO ADVISORY ACTION

The Examiner has stated that the proposed amendments submitted in Applicants' July 7, 2003 Response (Paper No. 18) were not entered because they raise new issues that would require further consideration and/or search and they present additional claims without canceling a corresponding number of finally rejected claims (*See*, Advisory Action). Specifically, the Examiner has stated that new claims 52-55, which Applicants attempted to add in the Amendment and Response filed on July 7, 2003, expand the scope of the claimed subject matter and would require additional search and examination (*See*, Continuation Sheet).

However, Applicants note with appreciation that the Examiner has indicated that newly proposed or amended claims 2-5 and 7-21, as submitted in Paper No. 18 would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s). Applicants thank the Examiner for this suggestion and respectfully request that the instant response, which amends claims 2 and 10-13 and adds claim 51, be entered. Applicants have withdrawn proposed claims 52-55, which were included in the July 7, 2003 Amendment and Response but reserve the right to pursue the subject matter of these claims in a later application.

REMARKS FROM JULY 7, 2003 AMENDMENT AND RESPONSE

As requested by the Examiner in the September 4, 2003 telephone conference held between Matthew Pavao, Agent for Applicants and the Examiner, for clarity purposes, Applicants have reiterated below the arguments regarding claims 2-5, 7-21 and new claim 51 that were previously presented in their July 7, 2003 (Paper No. 8) Response. The July 7, 2003 Response and Amendment (Paper No. 8) was timely filed in response to the May 7, 2003 Final Office Action. Specifically, Applicants have amended these arguments in order to remove reference to new claims 52-55.

THE 35 U.S.C. §102 REJECTIONS

The Examiner has maintained the rejection of claims 2, 5, 7-13 and 18-20 under 35 U.S.C. §102(b) as being anticipated by US Patent No. 5,629,159 ("Anderson") as evidenced by Kilby *et al.*, *Trends Genet.* 9: 413-421, 1993 ("Kilby"). Specifically, the Examiner states that claimed nucleic acid molecule has the same structural limitations as the nucleic acid molecule taught by Anderson. The Examiner also states that although Applicant's argument (that Anderson does not teach or suggest inversion of a recombinase gene or expression control sequence) is noted, the claims are not limited to inversion of a recombinase gene or expression control sequence (*see*, Office Action at page 4).

Applicants have herewith amended claims 2 and 10-13 to recite a nucleic acid molecule comprising a first and a second signal sequence that are positioned to mediate inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase, which decreases or eliminates recombinase-mediated toxicity. Anderson teaches the excision of an immortalization gene using a first and second recombinase signal sequence where the sequence can be LoxP or FRT. However, Anderson does not teach or suggest the inversion of either a recombinase gene or an expression control sequence. Kilby teaches that an excised nucleic acid would be quickly lost *in vivo*. Applicants note that Kilby alone or in combination with the teachings of Anderson, does not teach or suggest the inversion of either a recombinase gene or an expression control sequence or the decrease or elimination of recombinase-mediated toxicity following inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase.

Further, new claim 51 added herein is not anticipated by Anderson or Kilby. New claim 51 depends from claim 2 and therefore contains all the limitations of claim 2. Thus, neither Anderson nor Kilby, alone or in combination, teaches or suggests all of the limitations of the invention of new claim 51.

Thus, because Anderson and/or Kilby do not teach or suggest all of the limitations of the claimed invention. Applicants assert that claims 2 and 10-13, as amended herein (and claims 5, 7-9 and 18-20, which depend from claim 2) and new claim 51, as added herein, are not anticipated by Anderson as evidenced by Kilby. Therefore, this rejection of these claims should be withdrawn.

The Examiner has maintained the rejection of claims 2-4, 7 and 8 under 35 U.S.C. §102(b) as being anticipated by either one of WO 97/06271 ("Choulika") as evidenced by US Patent 6,200,800 ("Choulika '800") or Russ *et al., J. Virol.* 70(8): 4927-4932 ("Russ") as evidenced by Kilby. Specifically, the Examiner states that claimed nucleic acid molecule has the same structural limitations as the nucleic acid molecule taught by Choulika and Russ.

As discussed above, Applicants have amended claim 2 to recite a nucleic acid molecule comprising a first and a second signal sequence that are positioned to mediate inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase, which decreases or eliminates recombinase-mediated toxicity. Choulika and Russ teach a loxP site in the 3'LTR sequence U3 with the gene to be inserted into a cell. Choulika and Russ do not specifically teach the inversion of either a recombinase gene or of an expression control sequence. Moreover, Kilby teaches that an excised nucleic acid would be quickly lost *in vivo* and Choulika '800 teaches that a recombinase system can include CreLox sites or FLP sites. However, neither reference, alone or in combination with the teachings of Russ and Choulika, respectively, teaches or suggests the inversion of either a recombinase gene or an expression control sequence or the decrease or elimination of recombinase-mediated toxicity following inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase.

Further, new claim 51 added herein is not anticipated by Choulika as evidenced by Choulika '800 or Russ as evidenced by Kilby. New claim 51 depends from claim 2 and therefore contains all the limitations of claim 2. None of these references, alone or in combination, teach or suggest all of the limitations of the invention of new claim 51.

Accordingly, Applicants assert that claim 2, as amended herein (and claims 3-4, 7 and 8, which depend from claim 2) and new claim 51, as added herein, are not anticipated by Choulika

as evidenced by Choulika '800 or by Russ as evidenced by Kilby. Therefore, the rejection of these claims should be withdrawn.

The Examiner has also maintained the rejection of claims 2, 5, 7-13 and 18-20 under 35 U.S.C. §102(a) as being anticipated by Bunting *et al.*, *Genes & Development* 13(12): 1524-1528, 1999 ("Bunting") as evidenced by Kilby. Specifically, the Examiner states that the claimed nucleic acid molecule has the same structural limitations as the nucleic acid molecule taught by Bunting.

As discussed above, Applicants have amended claim 2 to recite a nucleic acid molecule comprising a first and a second signal sequence that are positioned to mediate inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase, which decreases or eliminates recombinase-mediated toxicity. Bunting teaches a nucleic acid molecule comprising a first and second recombinase signal sequence flanking a recombinase encoding sequence as well as the transformation of ES cells with such a described nucleic acid molecule. Bunting further teaches that a neomycin resistance gene can be positioned between the recombinase signal sequences such that expression of the recombinase excises the neomycin resistance gene. Bunting does not specifically teach the inversion of either a recombinase gene or of an expression control sequence. Kilby teaches that an excised nucleic acid would be quickly lost *in vivo*. Thus, Kilby, alone or in combination with the teachings of Bunting, does not teach or suggest the inversion of either a recombinase gene or an expression control sequence or the decrease or elimination of recombinase-mediated toxicity following inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase.

Further, new claim 51 added herein is not anticipated by Bunting or Kilby. New claim 51 depends from claim 2 and therefore contains all the limitations of claim 2. Thus, neither Bunting nor Kilby, alone or in combination, teaches or suggests all of the limitations of the invention of new claim 51.

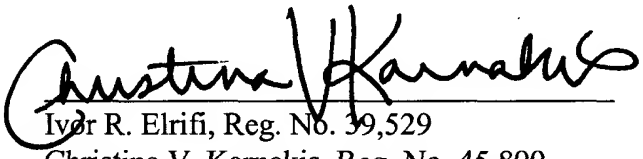
Thus, Bunting and/or Kilby do not teach all of the limitations of the claimed invention. Accordingly, Applicants assert that claim 2, as amended herein (and claims 5, 7-13 and 18-20,

which depend from claim 2) and new claim 51, as added herein, are not anticipated by Bunting as evidenced by Kilby. Therefore, this rejection of these claims should be withdrawn.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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